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(54) Implant preparations for delivery of bioactive macromolecules.

(57) Implant preparations capable of sustained action when inserted are comprised of powder of natural lipoidal substance in thorough admixture with bioactive macromolecule, followed by compression under pressure into a disc or rod that can be broken and used in small pieces as well.

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resulting in rapid decay to an inadequately low level a few hours later. To compensate for the decay, a second injection is required. Another remedy to correct the inconsistency is to infuse a dilute solution of the labile agent continuously at a low rate. The slow infusion can actually achieve a better outcome, because most active agents have a relatively short half-life in vivo or are toxic if the daily required dose is given at once by injection. However, the advantage of low-dose infusion is compromised by the incidence of infection and discomfort due to the presence of the indwelling needle and the catheter attachment. Therefore, extensive effort is continuing to find an implantable infusion device or preparation that can deliver an active agent for a prolonged period of time.

BRIEF REFERENCE TO THE PRIOR ART

In the early 1970's when the merit of giving a drug in small doses by continuous external infusion was demonstrated, further efforts were aimed at the development of implantable pumps and drug releasing capsules. Another purpose was to free the recipient of the chance of infection and provide total unrestrained mobility which often contributed immensely to the patient's sense of well being.

There have been several different designs of implantable pump under development during the past five years. But none has been long lasting without developing

demonstrated to be capable of promoting growth and reducing hyperglycemia for many weeks (Langer et al., Diabetes, 29 (1980) 37). But the device is non-absorbable in the body, and the long-term biological effect of the polymer material on the host still requires extensive evaluation.

In consideration of the aforementioned, an implant for delivery of bioactive macromolecule should be simple, so that it will be easy to fabricate and require no follow-up maintenance when implanted. Its size has to be small to avoid imposing excessive tension on the subcutaneous tissue due to stretching when the implant is inserted. The device should hold a sufficient amount of the bioactive macromolecule to sustain the desire effect for many weeks. As well, the excipient component should be absorbable by the body without adverse effect, so that no time consuming surgical procedure is needed to explant the depleted device later. Further, when the implant stopped functioning after a period of time, the incorporated active ingredient should be essentially depleted, so that a new absorbable implant can be inserted, if desired, to continue the regimen without interference from residual activity of the previous implant. Finally, it is important that no surge of the active ingredient should occur in the body causing overdose, if the implant is fractured.

macromolecule therein is considered to be insignificant, however, the present invention has found it to be otherwise. These lipoidal substances, being components of all animal cells and tissues, are varieties of water-insoluble compounds. For use in the present invention, lipoidal substances which are solid at room temperature are selected and made into powder form without any other special treatments aside from grinding in a mortar and pestle for a few minutes. Typical of such solid lipids are saturated fatty acids with 12 or more carbon atoms in the linear chain. The preferred fatty acids are lauric, myristic, palmitic, and stearic acids or a combination of these acids or derivatives. Their glycerides, as well as similar esters of their unsaturated equivalents, are also solids and readily available in abundance. However, simple esters of fatty acids and their corresponding alcohols are sometimes waxy substances which may be hardened and ground at low temperature into the powder form. Polar lipids that can be considered as well include phosphatidylethanolamine, phosphatidylcholine, sphingomyelin, phosphatidylserine, phosphatidylinositol, cardiolipin, galactocerebroside, glucocerebroside or the like. Among the solid steroid or steroid-like members of the solid lipids, the carotenes, vitamins D and K, cholic acids, coprostanol, and cholesterol are readily available in the powder form. The preferred steroidal lipid is cholesterol which is practically

pellet disc of the present invention may be determined to some extent by trials in vivo using different sizes of the insulin containing disc. Therefore, if a lesser amount is desired daily, it can be achieved by implanting a small piece cut from the pellet disc. Otherwise, a slightly larger piece may be used to provide a higher daily dose, if required.

The invention is further described by the following specific examples, which are presented as illustrations, and not intended to limit the scope of the present invention.

EXAMPLE

An amount of 160 mg of powdered palmitic acid and 40 mg of powdered bovine insulin (24 IU/mg) are first mixed in a 4 cm by 4 cm plastic weighing boat. The mixed powder is then transferred into a 1.5-mL capacity plastic vial with cap and a stainless steel bearing ball is added to aid mixing. The capped vial is pressed onto the platform of a vortex mixer (Vortex-Genie Mixer Catalogue number 12-812, Fisher Scientific Co., Toronto) turned to its maximum speed. After 2 min on the mixer, all the well-mixed powder is carefully tapped into the well of the Spex 13-mm die (Spex Industries, Inc., Edison NJ) without the bearing ball. After the plunger component is lowered into the well, the die set is placed in the centre of the hydraulic press (Spex-Carver Model C, Spex Industries, Inc.). A moderate compression of

Ontario). Meanwhile, the timer on the Glucometer^R (Colorimeter for Dextrostik^R, Miles Lab.) is activated, and after 60 sec when the alarm has sounded, the blood layer is thoroughly washed off from the Dextrostix^R. The intensity of the blue color on the tip is a measure of the blood glucose level in the sample and can be determined quantitatively by inserting the developed Dextrostik^R into the Glucometer^R, which will show the glucose content on its indicator display in mM glucose/L blood. The results show that the healthy control has a range of about 6-11 mM glucose/L, while the diabetics have a value exceeding 22 mM/L, on the day after streptozotocin injection, which is the maximum limit that can be read on the Glucometer^R. On the 8th day after the induction of hyperglycemia, 1 of the diabetic animals in the third group is implanted subcutaneously near the abdomen with 1/8 of the standard size pellet disc prepared as just described. A diabetic rat of body weight between 300-400 g requires about 3 IU insulin daily to lower the blood glucose level to the normal range of 6-11 mM/L. In the 1/8 portion of the standard size pellet disc, there is 5.0 mg insulin or a total of 120 IU, which should be sufficient to supply the need for 40 days. The remaining diabetic animal in the third group is implanted subcutaneously with 1/4 of the standard size pellet disc. The 1/4 disc contains enough insulin to reduce hyperglycemia for about 80 days. The blood sugar level for

As shown in the last 2 columns of Table 1, reduction in the blood glucose level was observed the next day indicating the fast onset of action. The test animals also continued to gain weight when checked at the time of taking blood samples. In the 30-day period, the diabetic animal with implant in the 3rd Group-A gained 57 g, and the other diabetic animal in the 3rd Group-B gained 82 g during the time when the implant was functional for about 40 days. The healthy control animal in the 1st Group gained body weight steadily as expected, but the diabetic control in the 2nd Group lost 45 g after 38 days and it appeared emaciated as well as stunted.

Hyperglycemia recurred on the 32nd day of the calculated 40 day service life of the 1/8 disc implanted in the diabetic rat of the 3rd Group-A. For the 1/4 disc in the 3rd Group-B of another diabetic animal, the preparation implanted functioned well until the 40th day of the calculated 80-day supply of insulin. Since the blood glucose values monitored over the period were lower than the healthy control group, the implants in the 3rd Group of diabetic animals might have received more than the postulated 3 IU/day which would account for the shorter service life actually observed. Since the implant in the animal of the 3rd Group-B was double in size as compared to the other without showing ill effects, the results also demonstrated the margin of safety in the use of the

of about 4 mg. This amount of insulin has a total activity of about 100 IU. At a demand of about 3 IU/day, it is expected to reduce hyperglycemia in the diabetic rat for 33 days. The test animal is bled according to the schedule shown in Table 2, and the Glucometer^{R} method is used to determine the glucose level as in Example 1.

Table 2

Lowering of Blood Glucose in Diabetic Rat by Inserted Insulin Containing Chips

Duration (days)	Blood Glucose (mM/L)
(no chips inserted)	
0	>22
(chips inserted)	
1	3.0
2	2.4
3	2.7
4	3.0
7	2.8
10	3.8
15	3.1
21	2.9
28	2.9
34	20.1
36	>22
40	>22

The results obtained show that even when the pellet disc is sub-divided into fragments, there is no unexpected overdoes of the incorporated insulin. The same hyperglycemia reduction is again achieved in comparison to the larger pieces of the pellet disc as described in Example 1. However, the duration of maintenance is still consistent

Table 3
Cumulative Amount of Somatotropin in Solution Derived from Pieces of Pellet Disc

Duration (days)	Hormone in Solution (mg/L)
1	1.1
3	3.8
5	6.0
8	9.2
10	10.9
12	13.0
15	17.5
17	18.2
19	21.1
22	25.0
24	26.1
26	27.4
29	31.3
31	34.9
34	36.5
36	36.1
40	36.4

The results showed that >90% of the polypeptide hormone entered the stirred solution gradually for a period of over 4 weeks. If more somatotropin is required daily, its content in the pellet disc can be slightly increased. For implantation to promote growth, no antigenic problem will develop if the preparation is used in an isogenic recipient, especially when the excipient components chosen are natural lipid materials present in all tissues.

From the preceding examples, it is thus seen that the objects set forth above are efficiently attained. Since changes may be made in carrying out the above described process and in the article set forth without departing from the scope of the invention, it will be understood that the above examples are illustrative only, and the invention is not limited thereto.

(5) A process of Claim 4 wherein the amount of somatotropin comprises about 1% to about 50% by weight, with the balance being the lipid material which includes glycerides selected from glyceryl esters of lauric, myristic, palmitic, stearic, oleic, linoleic acids or combination thereof; long-chain fatty acids or derivative selected from lauric, myristic, palmitic, stearic, oleic, linoleic acids, their simple esters, salts, amides, anhydrides, or combination thereof; and non-hormonal steroids selected from coprostanol, cholesterol, cholic acid, their esters, simple glycosides or combination thereof.

(6) A bioerodibe preparation suitable as implant with sustained action which comprises a compressed admixture of an effective amount of bioactive macromolecule and lipid powder with the said lipid powder being selected from glycerides, waxes, long-chain fatty acids or derivatives, sphingolipids, cerebrosides, terpenes, non-hormonal steroids or a combination thereof.

(7) A bioerodible preparation of Claim 6 with sustained action capable of continuously reducing diabetic hyperglycemia for a prolonged period of time and promoting growth upon implantation wherein said bioactive macromolecule is insulin.

(8) A bioerodible preparation of Claim 7 wherein the amount of insulin comprises about 11% to about 40% by weight with the balance being the lipid materials which includes

(12) A kit for preparing a bioerodible preparation as claimed in Claim 8 and Claim 10 which comprises the bioactive macromolecule and the lipid material.

(13) A method of sustaining the action of bioactive macromolecule preparation which comprises of compressing powder admixture of effective amount of bioactive macromolecule and lipid material selected from glycerides, waxes, long-chain fatty acids or derivatives, phospholipids, sphingolipids, cerebrosides, terpenes, nonhormonal steroids or combination thereof.

(14) A method of sustaining the action of bioactive macromolecule preparation as claimed in Claim 13 wherein the bioactive macromolecule is insulin.

(15) A method of sustaining the action of bioactive macromolecule preparation as claimed in Claim 14 wherein the amount of insulin is about 11% to about 40% by weight with the balance being the lipid material including glycerides selected from glyceryl esters of lauric, myristic, palmitic, stearic, oleic, linoleic acids or combination thereof; long-chain fatty acids or derivatives selected from lauric, myristic, palmitic, stearic, oleic, linoleic acids, their simple esters, salts, amides, anhydrides or combination thereof.

(16) A method of sustaining the action of bioactive macromolecule preparation as claimed in Claim 13 wherein the bioactive macromolecule is somatotropin.

derivatives selected from lauric, myristic, palmitic, stearic, oleic, linoleic acids, their simple esters, salts, amides, anhydirdes or combination thereof; and non-hormonal steroids selected from coprostanol, cholesterol, cholic acid, their esters, simple glycosides or combination thereof.

(20) A method of promoting growth which comprises implanting a compressed powder admixture of effective amount of the growth hormone somatotropin in lipid materials selected from glycerides, waxes, long-chain fatty acids or derivatives, phospholipids, sphingolipids, cerebrosides, terpenes, non-hormonal steroids or combination thereof.

(21) A method of promoting growth as claimed in Claim 20 wherein the amount of somtotropin comprises about 1% to about 50% by weight with the balance being the lipid material which includes glycerides selected from glyceryl esters of lauric, myristic, palmitic, stearic, oleic, linoleic acids or combination thereof; long-chain fatty acids or derivatives selected from lauric, myristic, palmitic, stearic, oleic, linoleic acids, their simple esters, salts, amides, anhydrides, or combination thereof; and non-hormonal steroids selected from coprostanol, cholesterol, cholic acid, their esters, simple glycosides or combination thereof.

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PARTIAL EUROPEAN SEARCH REPORT

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	* Abstract *	1	
A	PHARMACEUTICA ACTA HELVETIAE, vol. 56, no. 4,5, 1981 Zürich, CH; E. DOELKER et al.: "Formulation des comprimés à libération prolongée III. Matrices lipidiques" * Whole document *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)